Published in final edited form as:
Nature. 2011 February 10; 470(7333): 245–249. doi:10.1038/nature09723.

Asymmetric Additions to Dienes Catalyzed by a Dithiophosphoric Acid

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Abstract

Chiral Brønsted acids have become an invaluable tool for achieving a variety of asymmetric chemical transformations under catalytic conditions while avoiding the use of toxic and expensive metals[1–8]. While the catalysts developed so far are remarkably effective at activating polarized functional groups, chemists have not yet been able to use organic Brønsted acids to catalyze highly enantioselective transformations of unactivated carbon-carbon multiple bonds. This deficiency persists despite the fact that racemic acid-catalyzed "Markovnikov" additions to olefins are a well-established part of the chemist's toolbox. Here we show that chiral dithiophosphoric acids catalyze the intramolecular hydroamination and hydroarylation of dienes and allenes to generate heterocyclic products in exceptional yield and enantiomeric excess. To help rationalize the unique success of this catalytic system, we present a mechanistic hypothesis that involves the addition of the acid catalyst to the diene followed by S_N2' displacement of the resulting dithiophosphate intermediate. Mass spectrometry and deuterium labelling studies are presented in support of the proposed mechanism. The catalysts and concepts revealed in this study should prove applicable to other asymmetric functionalizations of unsaturated systems.

It has been known for over a century that strong Brønsted acids can catalyze the addition of alcohols and other protic nucleophiles to simple olefins. The ability to predict the regioselectivity of these reactions is taught in every introductory organic chemistry course as Markovnikov's rule. However, successful approaches to asymmetric variants have relied on metal catalysts rather than organic Brønsted acids, particularly in the area of amine addition reactions[9–12]. Although metal-free Brønsted acids can catalyze additions to unactivated olefins with yields comparable to metals[13–15], the lone example of an attempted enantioselective variant of this reaction using a chiral acid resulted in poor selectivity (17%

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Supplementary Information accompanies the paper on www.nature.com/nature.

Author Contributions N.D.S. initiated the hydroamination study. V.R. optimized the catalysts and initiated the hydroarylation study. N.D.S., V.R., G.L.H. and J.W. performed the experiments. N.D.S., G.L.H., and F.D.T. developed the mechanistic concepts. G.L.H. and N.D.S. wrote the manuscript with input from all authors.

X-ray crystallographic data have been deposited into the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under code CCDC 800545.

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enantiomeric excess)[16]. Although a number of structurally diverse strong Brønsted acid catalysts have been developed, the highly enantioselective reactions reported to date are restricted to the activation of an electrophilic carbon-heteroatom or heteroatom-heteroatom multiple bond, usually an imine or a carbonyl[1–8].

This unfortunate limitation can perhaps be explained by considering the different intermediates generated by protonation of an imine or carbonyl versus an olefin (Fig. 1A). Protonation of an imine or carbonyl generates a species that can hydrogen bond with the conjugate base of the chiral Brønsted acid. This hydrogen bond serves as an anchor to keep the chiral information close to the reactive electrophile and also contributes to the molecular organization that favours one particular diastereomeric transition state. On the other hand, protonation of an olefin leads to a carbocation. Although the conjugate base of the chiral acid can still be held in proximity to the carbocation through electrostatic interactions, the lack of rigidity in this association presumably results in poor discrimination between the enantiotopic faces of the carbocation. In fact, a recent review on chiral Brønsted acid catalysis goes as far as to say that "The key to realizing enantioselective catalysis using a chiral Brønsted acid is the hydrogen bonding interaction between a protonated substrate and the chiral conjugate base"[3]. Clearly, a conceptually different approach is needed to achieve the desired enantioselective additions to olefins.

We considered that this problem could be overcome for nucleophilic additions to dienes by using a chiral Brønsted acid with a nucleophilic conjugate base that could form a covalent bond with the carbocation (Fig. 1B). In a second step, the nucleophile could displace the chiral leaving group in S_N2' fashion. Because the chiral catalyst is directly bound to the substrate in the nucleophilic addition step, we hypothesized that this mechanistic scenario might facilitate a highly enantioselective transformation. Notably, two of the most important modes of organocatalysis, enamine and iminium catalysis, also take advantage of "covalent catalysis" mechanisms.[17]

A challenge in implementing such a strategy is finding an acid that is strong enough to protonate an olefin but also possesses a nucleophilic conjugate base. We considered that dithiophosphoric acids might be ideal candidates to fulfil both criteria[18]. The increased polarizability of sulfur (2.90) versus oxygen (0.802) makes dithiophosphoric acids more acidic and nucleophilic than their oxygenated analogs[19–21]. For the purpose of our desired reaction, it was promising to note that the addition of achiral dithiophosphoric acids to dienes is known to proceed efficiently with Markovnikov regioselectivity under radical free conditions[22]. We suspected that the challenge in reaction development would therefore arise in achieving a highly selective reaction, especially given that the single previously reported reaction using a chiral dithiophosphoric acid catalyst proceeded with low diastereo- and enantioselectivity (7:3 dr, 63% ee)[23]

Putting our idea into practice, we found that chiral dithiophosphoric acid **3a** catalyzed the intramolecular hydroamination of diene **1** to form the desired pyrrolidine product **2** with excellent yield and moderate enantioselectivity (Table 1, entry 1). As expected, the oxygenated phosphoric acid analogue **3b** did not promote the reaction at all (entry 2). We also found that an *N*-triflyl thiophosphoramide catalyst of the type reported by Yamamoto[6] catalyzed the reaction with comparable ee (entry 3), while the corresponding oxygen analogue **3d** did not give any desired product (entry 4). Attempts to optimize the catalyst structure by synthesizing more sterically encumbered *N*-triflyl thiophosphoramides resulted in unacceptably low yields, so we continued our investigation with dithiophosphoric acids.

Changing the 3,3′ substituents to bulkier anthracenyl groups led to a substantial boost in enantioselectivity, as did using a catalyst with a partially hydrogenated backbone (entry 5). We also noted that performing the reaction in fluorobenzene as solvent in the presence of 4A molecular sieves at a slightly reduced temperature (15 oC) further improved the selectivity (entry 6). Finally, based on the proposed S_N2'-type mechanism in which the incoming nucleophile is some distance away from the chiral dithiophosphate, we hypothesized that extending the catalyst structure could lead to even better results by more effectively "projecting" the chiral information. Consistent with this proposal, addition of an aromatic substituent at the 10-position of the anthracene moiety allowed us to achieve excellent enantioselectivity (entries 7–9). Notably, the mesityl catalyst **3h** provided exceptional enantioinduction even at room temperature. Because in some cases one catalyst offered slightly better selectivity than the other, we used both **3g** and **3h** for exploring the scope of the reaction.

A number of structural modifications could be made to the substrates while preserving the excellent yield and enantioselectivity of the catalytic hydroamination (Table 2). The sulfonyl group on the amine can be varied while maintaining the excellent yield and enantioselectivity of the reaction (entries 1 and 2). The terminal olefin can also be freely substituted with cyclic or acyclic groups (entries 3 and 4). Diene **4d** showed selectivity for the *E*-isomer of the product, although both geometric isomers were formed with high enantioselectivity and had the same absolute configuration at the newly formed stereogenic centre. Interestingly, complementary selectivity for the *Z*-olefin could be achieved by using the isomeric diene **4e** (entry 5). In both cases, the major product was obtained in higher enantiomeric excess than the other olefin isomer. With regard to functional group tolerance, it is remarkable to note that a primary *tert*-butyldimethylsilyl (TBS) ether was stable in the presence of the strongly acidic catalyst in spite of the general acid lability of this protecting group (entry 6). The tendency of the dithiophosphate to add covalently to the diene rather than remain free in solution may explain this surprising chemoselectivity. Additionally, the tether between the nucleophile and the diene can be varied to generate spirocyclic products (entries 7 and 8).

In considering our mechanistic hypothesis, we realized that we should be able to access the same type of allylic dithiophosphate ester intermediate from addition of the Brønsted acid catalyst to allenes (1,2-dienes). We found that allene substrate **4i** was indeed converted to the pyrrolidine product **2** with essentially the same yield and enantioselectivity as was observed starting from the corresponding 1,3-diene (Table 2 entry 9, cf. Table 1 entry 8). This observation also held true for other substrates. Although sulfonyl-pyrrolidines are themselves useful compounds from a medicinal chemistry standpoint[24,25], we also wanted to prepare products where the nitrogen substituent could be cleaved under mild conditions. Toward this end, we found that a nosyl-protected amine could be synthesized with only a modest decrease in enantioselectivity (entry 10, 90% ee). Perhaps unsurprisingly, a more drastic change to a phosphinyl protecting group resulted in a slightly greater drop in selectivity (entry 11). Hydroxylamines also proved to be useful substrates for the reaction, providing isoxazolidine products with very good enantioselectivities (entries 13 and 14). Although in general we obtained the best results with substrates that possess geminal disubstitution in the alkyl tether, an observation likely attributable to the Thorpe-Ingold effect, the high enantioselectivity obtained using allene **4n** demonstrates that this is not strictly necessary for the success of our reaction.

A number of additional experiments were performed in order to further elucidate the mechanism of this transformation (Fig. 2). We began by analyzing aliquots taken during the course of the catalytic reaction of **1** using time-of-flight mass spectrometry (TOF-MS). A new peak that was fully consistent (*m/z* and isotopic distribution) with proposed intermediate **6** was observed (Fig. 2A, Supporting Figs. 4 and 5). The proposed formation of this intermediate is also supported by the fact that the addition of dithiophosphoric acids across alkenes and dienes is a well-established process[20,22,26,27].

An investigation of the diastereoselectivity of the protonation and nucleophilic addition steps revealed some more insights regarding the mechanism. A deuterated achiral dithiophosphinic acid added across acenaphthylene, a cyclic olefin often used as a stereochemical probe, with a very high level of *syn*-stereoselectivity (Fig. 2B). No epimerization of the product was observed even after a prolonged reaction time with heating (50 °C, 72 h). Thus, at least in this case, the dithiophosphinate ester intermediate does not ionize under conditions harsher than those used in the catalytic reaction. We next examined the reaction of a cyclic diene-tethered sulfonamide substrate using a deuterated racemic catalyst (Fig. 2C). The obtained spirocyclic product was substantially enriched (4:1 dr) in the isomer where the sulfonamide nucleophile and the deuterium have a *cis* orientation. Taken together, these two experiments suggest that this observed *syn* diastereoselectivity is a result of initial *syn*-addition of the dithiophosphoric acid across the distal olefin, followed by a *syn*-S_N2' displacement (Fig 2D). Excluding metal-mediated processes, S_N2' reactions are known to proceed preferentially though *syn* pathways[28,29].

At this point we cannot say with certainty as to the degree of bonding between the nucleophile, allylic system, and dithiophosphate in the S_N2' displacement step. This step may be concerted, or it may involve the formation of an allylic carbocation-dithiophosphate tight ion pair that is rapidly trapped by the tethered sulfonamide. In either mechanism, the remarkable feature is that the catalyst is able to mediate the attack of the nucleophile on the carbon electrophile with sufficient organization to greatly favor one diastereomeric transition state. In addition, it should be noted that cyclization of stereochemical probe **8** using catalytic deuterated triflic acid proceeds with no diastereoselectivity (Fig. 2C). This result strongly supports the notion that the dithiophosphoric acid catalyzed reaction is mechanistically distinct from simple Brønsted acid catalysis.

To demonstrate the generality of this approach, we examined indoles as useful carbon nucleophiles that would be structurally and mechanistically distinct from the sulfonamides used in the rest of the study. Although a large number of efficient additions of indoles to imine and unsaturated carbonyl derivatives have been discovered, the envisioned organocatalytic enantioselective hydroarylation of an unactivated carbon unsaturated system has not been demonstrated[30]. When indole substrates were subjected to our reaction conditions, the hydroarylations proceeded readily to afford the tetrahydrocarbazole products in good to excellent enantiomeric excess (80–91% ee) (Fig. 2E). An X-ray structure of a crystalline sample of the brominated derivative confirmed the structure and revealed the absolute configuration of the products (Supplementary Figure 11 and Supplementary Table 1).

The high enantioselectivity of this carbon-carbon bond forming reaction is particularly striking because the N-alkylated indole substrates do not possess any apparent hydrogen bond donors to assist in the catalyst-substrate organization. As previously mentioned, the presence of hydrogen bonding functionality has been a signature of nearly all of the previously demonstrated chiral Brønsted acid catalyzed reactions[3]. It is possible that in our system, the covalent attachment of the catalyst eliminates the need for the hydrogen bonding that is typically required for reactions that proceed by an ion pair mechanism. We believe the applicability of these catalysts and concepts to this different type of bond formation augurs well for the scope of future developments.

In spite of the remarkable developments in the field of asymmetric catalysis, there are still a great number of important transformations that are beyond the reach of current synthetic approaches. We have reported here a method using dithiophosphoric acids that enables metal-free catalytic asymmetric nucleophilic additions to all-carbon π-systems. In addition to serving as a useful means of obtaining valuable chiral hetero- and carbo-cyclic products, the hydroamination and hydroarylation of dienes are fundamentally distinct from those that have been previously achieved using chiral organocatalysts. Finally, we have presented experimental evidence that is most consistent with a unique covalent catalysis mechanism.

Methods Summary

General procedure: to a 1-dram screw cap vial was added the diene or the allene substrate (0.1 mmol, 1.0 equiv) followed by the dithiophosphoric acid catalyst **3f, 3g** or **3h** (0.01 mmol, 0.1 equiv) and activated 4 Å molecular sieves (20 mg). To the mixture was added fluorobenzene (0.5 mL) at room temperature. The vial was sealed and allowed to stand for 48 h at the indicated temperature. After the reaction was complete, the entire mixture was loaded onto silica gel and the product was eluted with EtOAc/hexanes. For complete experimental details, including procedures and full characterization (^{1}H and ^{13}C NMR, HRMS) of all new compounds, see the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Diego Benitez and Ekaterina Tkatchouk (Goddard Group, California Institute of Technology) for performing DFT calculations, to Dr. Ulla Anderson and Dr. Tony Iavarone of the QB3/Chemistry Mass Spectrometry Facility, and to Dr. Antonio DiPasquale of the X-ray Crystallography Facility. We acknowledge funding from the Director, Office of Science of the U.S. Department of Energy under Contract No. DE-

AC02-05CH11231 and NIHGMS (R01 GM074774). V.R. is grateful for a Natural Sciences and Engineering Research Council of Canada (NSERC) postdoctoral fellowship. G.L.H. is grateful for a Bristol-Myers/Squibb graduate fellowship.

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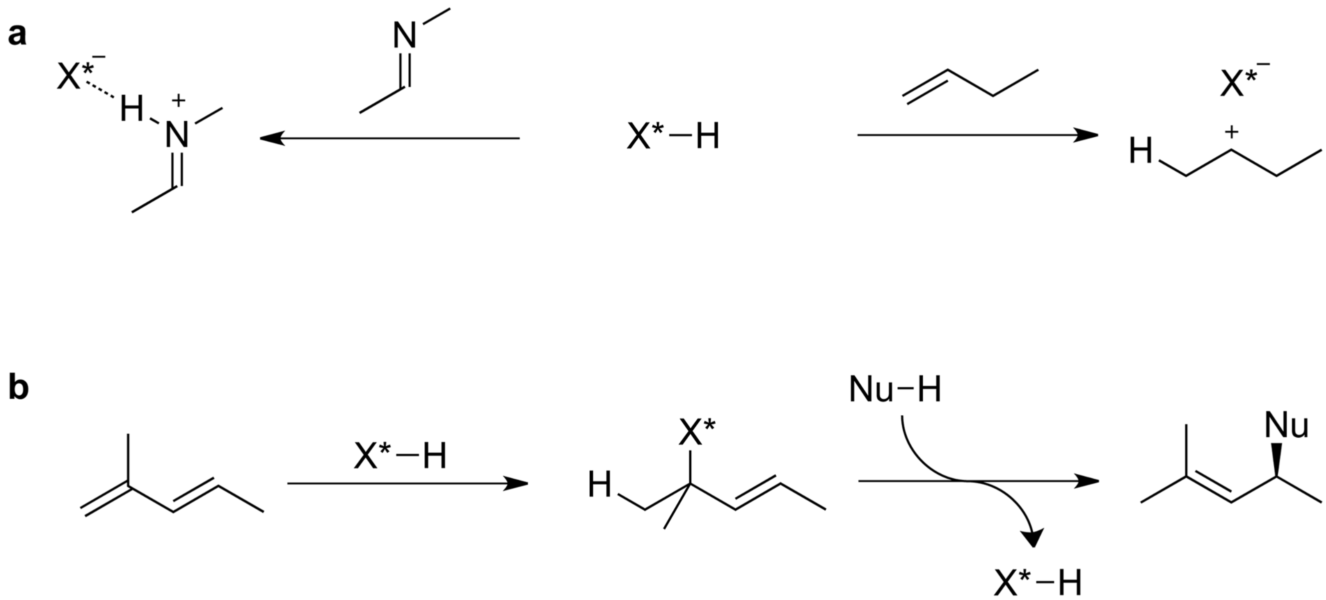

Figure 1. A possible solution to the mechanistic challenge of asymmetric acid-catalyzed additions to olefins

(a) Protonation of an imine with a chiral Brønsted acid (X*–H) leads to a hydrogen bonded intermediate, while protonation of an olefin results in a carbocation that cannot form a hydrogen bond. **(b)** Proposed mechanism wherein a nucleophilic chiral acid adds to a diene then undergoes enantioselective S_N2' displacement.

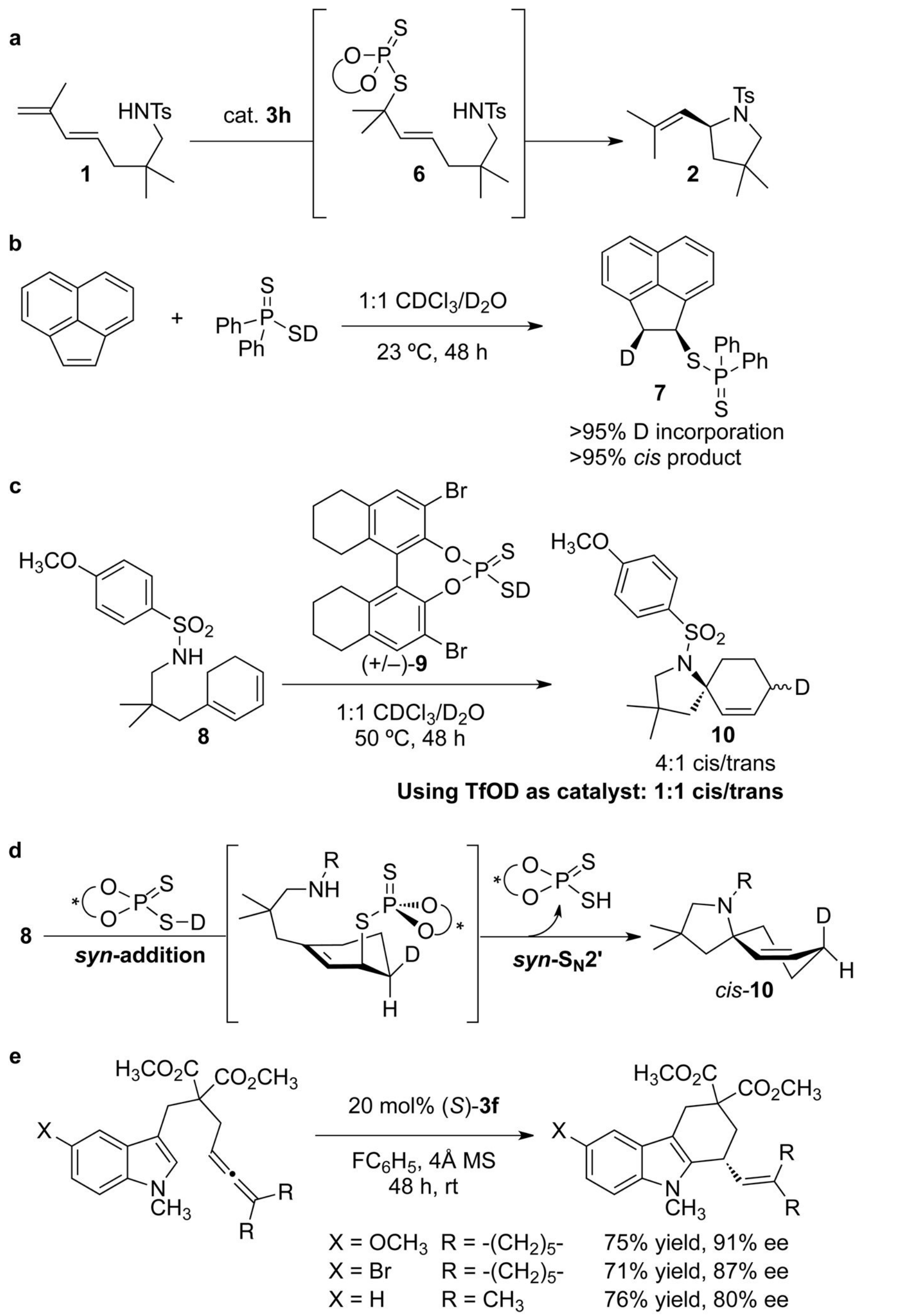

Figure 2. Experiments to elucidate the reaction mechanism and application to indole nucleophiles

(a) Proposed reaction mechanism involving a covalently bound catalyst-substrate intermediate that undergoes S_N2' displacement. **(b)** Addition of an achiral dithiophosphinic acid across an olefin proceeds with *syn* stereoselectivity. **(c)** Reaction of a cyclic substrate using deuterated catalyst reveals 1,4-*syn*-stereoselectivity. **(d)** The overall mechanistic picture suggested by these experiments involves initial *syn*-addition of the S-H(D) bond across the olefin, followed by *syn*-S_N2' displacement. R = $SO_2(4\text{-}CH_3O\text{-}C_6H_4)$. **(e)**

Dithiophosphoric acid-catalyzed hydroarylation of indole derivatives; MS = molecular sieves.

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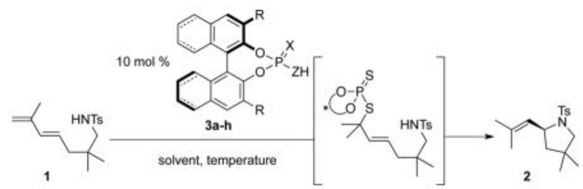
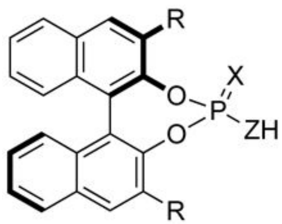
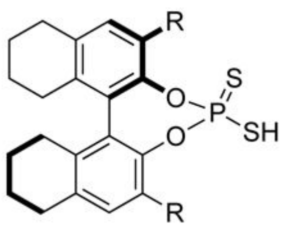
Table 1

Optimization of the reaction conditions of the asymmetric hydroamination.

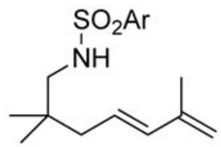
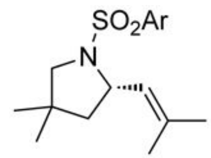
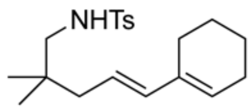
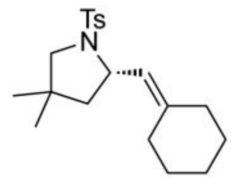
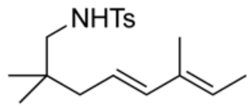
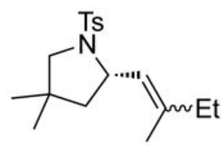
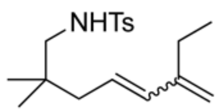
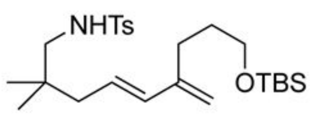
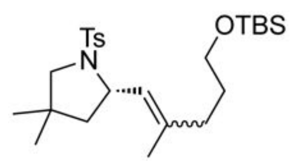


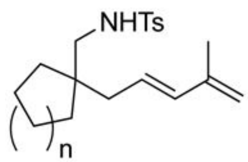
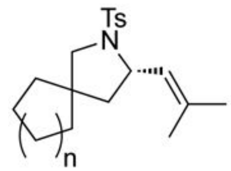
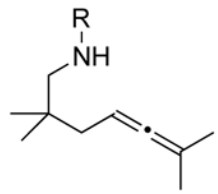
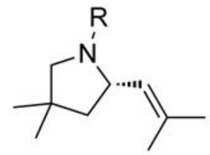
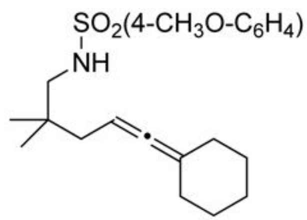
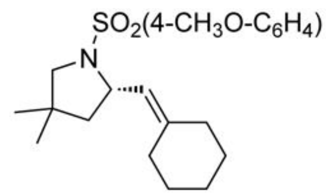
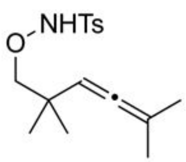
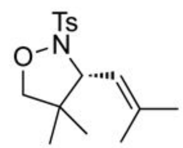
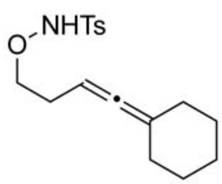
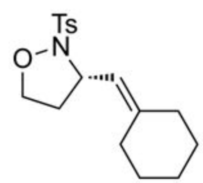
entry	catalyst			solvent, temp.	% yield	% ee
1		**3a**	X = Z = S, R = 1-naphthyl	$CDCl_3$, 30 °C	91	41
2		**3b**	X = Z = O, R = 1-naphthyl	$CDCl_3$, 30 °C	0	N/A
3		**3c**	X = S, Z = NTf, R = 1-naphthyl	$CDCl_3$, 30 °C	89	46
4		**3d**	X = O, Z = NTf, R = 1-naphthyl	$CDCl_3$, 30 °C	0	N/A
5		**3e**	R = 9-anthracenyl	$CDCl_3$, 30 °C	98	62
6		**3e**	R = 9-anthracenyl	FC_6H_5, 15 °C	91	78
7		**3f**	R = 10-(C_6H_5)-anthracenyl	FC_6H_5, 15 °C	92	94
8		**3g**	R = 10-(3,5-bis-*t*-Bu-C_6H_3)-9-anthracenyl	FC_6H_5, 15 °C	96	96
9		**3h**	R = 10-(2,4,6-$(CH_3)_3$-C_6H_2)-9-anthracenyl	FC_6H_5, 23 °C	98	96

Ts = p-toluenesulfonyl; Tf = trifluoromethanesulfonyl. Reactions were all run for 48 h. Yields were determined by NMR analysis versus an internal standard; ee's were determined by chiral HPLC.

Table 2

Performance of various 1,2- and 1,3-dienes in the enantioselective hydroamination reaction.

entry	diene (4a–4i)		temp.	product (5a–5i)		% yield (*E*:*Z*)	% ee
1		**4a**	23 °C		**5a**	99	92
2	**4a:** Ar = 3,5-$(CH_3)_2C_6H_3$ **4b:** Ar = 4-Cl-C_6H_4	**4b**	23 °C		**5b**	99	95
3		**4c**	30 °C		**5c**	70	94
4		**4d**	30 °C		**5d**	90 (4.7:1)	95 (*E*) 90 (*Z*)
5	 6:1 *E*/*Z*	**4e**	23 °C		**5d**	75 (1:2)	99 (*Z*) 91 (*E*)
6		**4f**	23 °C		**5f**	91 (1:3.6)	99 (*Z*) 80(*E*)

entry	diene (4a–4i)		temp.	product (5a–5i)		% yield (*E*:*Z*)	% ee
7		**4g**	23 °C		**5g**	99	96
8	**4g:** n = 1 **4h:** n = 2	**4h**	23 °C		**5h**	91	97
9		**4i**	23 °C		**2**	99	95
10		**4j**	23 °C		**5j**	81	90
11	**4i:** R = Ts **4j:** R = Ns **4k:** R = $POPh_2$	**4k**	23 °C		**5k**	99	83
12		**4l**	40 °C		**5l**	67	97
13		**4m**	23 °C		**5m**	70	90
14		**4n**	60 °C		**5n**	67	92

TBS = *tert*-butyldimethylsilyl; Ns = 2-nitrophenylsulfonyl. Reactions were run in fluorobenzene for 48 h using 10 mol% **3g** (entries 3 and 4) or 10 mol% **3h** (all others, 20 mol% for entry 14) in the presence of 4A molecular sieves. Yields refer to isolated material.